Conclusion

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Respectfully submitted,

PILLSBURY WINTHROP LLP

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By: _____
John R. Wetherell, Jr., Ph.D.
Reg. No. 31,678

11682 El Camino Real, #200
San Diego, CA 92130
Tel. No.: (858) 509-4022
Fax No.: (858)509-4010

APOPTOSIS MODULATOR BCL-B AND METHODS FOR MAKING AND USING SAME

PRIORITY INFORMATION

This application was supported by NIH Grant GM60554 and by U.S. Army Medical Research and Material Command Grant DAMD17-99-1-9511. This application claims priority to U.S. application serial no. 60/267,166, filed February 7, 2001.

TECHNICAL FIELD

This invention generally relates to cell and molecular biology and the regulation of cell proliferation, apoptosis and survival. In particular, the invention provides polypeptides comprising apoptosis modulator Bcl-B, a Bcl-2 family member, nucleic acids encoding the polypeptides, and methods for making and using these compositions, including, for example, modulating cell apoptosis, survival, proliferation.

BACKGROUND

Programmed cell death or apoptosis is a cellular suicide process in which damaged or harmful cells are eliminated from multicellular organisms. Cells undergoing apoptosis have distinct morphological changes including cell shrinkage, membrane blebbing, chromatin condensation, apoptotic body formation and protein and nucleic acid fragmentation. This cellular suicide program is evolutionarily conserved across animal and plant species.

Apoptosis plays an important role in the development and homeostasis of metazoans and is also important for insect embryonic development and metamorphosis. Furthermore, apoptosis can act as a host defense mechanism. For example, apoptosis eliminates virally infected cells thereby limiting propagation of viruses. Apoptosis is also involved in plant reactions to biotic and abiotic insults. Moreover, dysregulation of apoptosis has been associated with a variety of human diseases including cell proliferative disorders (*e.g.*, cancer), cell degenerative disorders (*e.g.*, neurodegeneration, muscular degeneration, ischemia, stroke, etc.) and autoimmune diseases. Accordingly, identification of the components that modulate apoptosis provides a means to study and manipulate the process in a wide variety of organisms.

Programmed cell death is regulated by the interplay of proteins that inhibit and proteins that stimulate cell death or cell survival. Among the proteins that modulate apoptosis are the

Bcl-2 family members. Bcl-2 protein family members include proteins that promote and inhibit programmed cell death. Bcl-2 family proteins play a role in apoptosis regulation in metazoan species. In humans, over 20 Bcl-2 proteins have been identified to date, including proteins which suppress (Bcl-2, Bcl-XL, Mcl-1, Bfl-1/A1, Bcl-W) and proteins which promote (Bax, Bak, Bok, Bad, Bid, Bik, Bim, Nip3, Nix) cell death (Reed, J. *Oncogene* **17**, 3225-3236(1998); Reed, J. C. *Amer J Pathol* **157**, 1415-1430(2000)).

Bcl-2 family proteins contain at least one of four conserved regions, termed Bcl-2 Homology (BH) domains. Most members of this family also contain a transmembrane (TM) domain located near the carboxyl-terminus that anchors them in intracellular membranes of mitochondria and other organelles (Reed, J. *Oncogene* **17**, 3225-3236(1998); Reed, J. C. *Amer J Pathol* **157**, 1415-1430(2000)).

Many Bcl-2 family proteins are capable of physically interacting, forming homo- or hetero-dimers, and functioning as agonists or antagonists of each other (Reed, J. *Oncogene* **17**, 3225-3236 (1998); Reed, J. C. *Amer J Pathol* **157**, 1415-1430 (2000); Oltvai, Z. N., and Korsmeyer, S. J. *Cell* **79**, 189-192 (1994)). Specificity for interaction partners and tissue-specific patterns of expression combine to endow each Bcl-2 protein with a physiological role *in vivo*, resulting for example in highly diverse phenotypes when members of this multigene family are individually knocked-out in mice (Vaux, D. and Korsmeyer, S. *Cell* **96**, 245-254 (1999)).

Thus, a need exists to identify members of the Bcl-2 family and to elucidate their functional characteristics. The present invention we describe the molecular cloning and initial characterization of a new human member of the Bcl-2 family, Bcl-B.

SUMMARY

The present invention is based in part on the identification and characterization of a novel member of the Bcl-2 family of apoptosis modulators, denoted Bcl-B. Bcl-B is capable of modulating apoptosis in cells. For example, Bcl-B inhibits apoptosis induced by Bax. Bcl-B also binds to itself as well as other modulators of apoptosis including, for example, Bax, Bcl-2 and Bcl-XL. Thus, Bcl-B is involved in apoptotic signaling as well as modulating activity or activation of other proteins, or having its own activity modulated by other proteins associated with programmed cell death. Accordingly, compositions of the invention, including, for example, Bcl-B polypeptides, polynucleotides, antibodies and subsequences thereof are useful for modulating apoptosis and associated signaling pathways, as well as for detecting Bcl-B (*e.g.*,